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S/N 10/583706 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	MITANI, et al.	Examiner:	Unknown
Serial No.:	10/583706	Group Art Unit:	Unknown
Filed:	June 20, 2006	Docket No.:	20078.0001USWO
Title:	METHOD OF AMPLIFYING NUCLEIC ACID AND METHOD OF DETECTING MUTATED NUCLEIC ACID USING THE SAME		

CERTIFICATE UNDER 37 CFR 1.6(d): I hereby certify that this paper is being transmitted by facsimile to the U.S. Patent and Trademark Office on March 22, 2007.
By: Peggy Kerkhove
Name: Peggy Kerkhove

REFUND REQUEST

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

Applicants hereby respectfully request a refund under 37 C.F.R. § 1.26. On March 20, 2007 Deposit Account No. 50-3478 was charged $400 (Fee Code 1642) for a National Stage Search Fee. Also on March 20, 2007, Deposit Account No. 50-3478 was charged $400 (Fee Code 1614) for extra independent claims (over three). Applicants respectfully state that the National Stage Search Fee and the independent claims fees were included in the check filed with this application. Enclosed is a copy of the Form 1390, as filed on June 20, 2006, which shows the complete breakdown of the fees paid. Therefore, Applicants respectfully request that the amount of $800 be refunded to Deposit Account No. 50-3478.

Applicants also respectfully request a refund of the $6650 (Fee Code 1615) and $360 (Fee Code 1616) which was charged to Deposit Account No. 50-3478 on March 20, 2007 in view of the Preliminary Amendment filed herewith.

Respectfully submitted,

52835
PATENT TRADEMARK OFFICE

HAMRE, SCHUMANN, MUELLER & LARSON, P.C.
P.O. Box 2902-0902
Minneapolis, MN 55402-0902
(612) 455-3800

Dated: March 22, 2007

By: _____
Douglas P. Mueller
Reg. No. 30,300

DPM/pjk

FORM PTO-1390 (REV 10-94) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 20078.1USWO

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5): Unknown

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP2004/019346	December 24, 2004	December 25, 2003

TITLE OF INVENTION

METHOD OF AMPLIFYING NUCLEIC ACID AND METHOD OF DETECTING MUTATED NUCLEIC ACID USING THE SAME

APPLICANT(S) FOR DO/EO/US

MITANI, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [ ] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US)
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An unsigned oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98, Form 1449, references.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information: Application Data Sheet, Communication Regarding Requested Figure, paper copy of Sequence Listing, computer readable form of the Sequence Listing, International Publication Page, Form PCT/ISA/210, Form PCT/IB/306

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
Unknown	PCT/JP2004/019346	20078.1USWO

BASIC NATIONAL FEE (37 CFR 1.492(a) (1)-(5)):		
[X] a) Basic National fee.....$300.00	$300.00	
[X] b) Examination fee.....$200.00	$200.00	
[X] c) Search fee.....$500.00	$500.00 *	
TOTAL OF ABOVE CALCULATIONS =	$1000.00	
[X] Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing or computer program listing filed in an electronic medium). The fee is $250 for each additional 50 sheets of paper or fraction thereof.		

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof (round up to a whole number	Rate		
106 -100 =	1 /50 =	1	X $250.00	$250.00	
Surcharge of $130.00 for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$	

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE		
Total claims	83	-20 =	63	X $50.00	$3150.00	
Independent claims	8	-3 =	5	X $200.00	$1000.00 *	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ $360.00	$	
TOTAL OF ABOVE CALCULATIONS =					$5400.00	
Reduction by 1/2 for filing by small entity, if applicable. Small entity status is claimed pursuant to 37 CFR 1.27					$	
SUBTOTAL =					$5400.00	
Processing fee of $130.00 for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f).				+	$	
TOTAL NATIONAL FEE =					$5400.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property				+	$	
TOTAL FEES ENCLOSED =					$5400.00	
				Amount to be: refunded	$	
				charged	$	

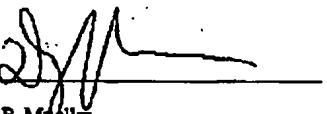
a. [X] Check(s) in the amount of $5,400 to cover the above fees is enclosed.

b. [ ] Please charge the amount of $ to cover the required filing fee for a large entity to the credit card listed on the enclosed credit card authorization form.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-3478.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
Douglas P. Mueller
Haugen, Schumann, Mueller & Larson, P.C.
P.O. Box 2902-0902
Minneapolis, MN 55402

SIGNATURE: 

NAME: Douglas P. Mueller

REGISTRATION NUMBER: 30,300

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By: Peggy Kerkhove
Name: Peggy Kerkhove

PRELIMINARY AMENDMENT

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In connection with the above-identified application filed herewith, please enter the following preliminary amendment:

Amendments to the Claims are reflected in the listing of claims that begins on page 2 of this paper.

Remarks begin on page 16 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (ORIGINAL) A primer set comprising at least two primers that allows a target nucleic acid sequence to be amplified,

wherein a first primer included in the primer set contains, in its 3' end portion, a sequence (Ac') that hybridizes to a sequence (A) located in the 3' end portion of the target nucleic acid sequence, and also contains, on the 5' side of the sequence (Ac'), a sequence (B') that hybridizes to a complementary sequence (Bc) to a sequence (B) that is present on the 5' side with respect to the sequence (A) in the target nucleic acid sequence, and

a second primer included in the primer set contains, in its 3' end portion, a sequence (Cc') that hybridizes to a sequence (C) located in the 3' end portion of a complementary sequence to the target nucleic acid sequence, and also contains, on the 5' side of the sequence (Cc'), a folded sequence (D-Dc') that contains, on the same strand, two nucleic acid sequences that hybridize to each other.

2. (ORIGINAL) The primer set according to claim 1, further comprising a third primer that hybridizes to the target nucleic acid sequence or the complementary sequence thereto,

wherein the third primer does not compete with other primers for hybridization to the target nucleic acid sequence or the complementary sequence thereto.

3. (ORIGINAL) The primer set according to claim 1, wherein in the first primer, when no intervening sequence is present between the sequence (Ac') and the sequence (B'), a ratio $(X-Y)/X$ is in a range of −1.00 to 1.00, where X denotes the number of bases contained in the sequence (Ac') while Y indicates the number of bases contained in a region flanked by the sequence (A) and the sequence (B) in the target nucleic acid sequence, and when an intervening sequence is present between the sequence (Ac') and

the sequence (B') in the primer, a ratio $\{X-(Y-Y')\}/X$ is in a range of −1.00 to 1.00, where X and Y denote the same as described above, and Y' indicates the number of bases contained in the intervening sequence.

4. (ORIGINAL) The primer set according to claim 1, wherein in the second primer, the folded sequence (D-Dc') has a length of 2 to 1000 nucleotides.

5. (ORIGINAL) The primer set according to claim 1, wherein at least one primer included in the primer set has a solid-phase support or a site that can bind to a solid-phase support.

6. (ORIGINAL) The primer set according to claim 5, wherein the solid-phase support is one selected from the group consisting of a water-insoluble organic polymer support, a water-insoluble inorganic polymer support, a synthetic polymer support, a phase transition support, a metal colloid, and a magnetic particle.

7. (ORIGINAL) The primer set according to claim 5, wherein the site that can bind to a solid-phase support is selected from the group consisting of biotin, avidin, streptoavidin, an antigen, an antibody, a ligand, a receptor, a nucleic acid, and a protein.

8. (CURRENTLY AMENDED) A method of amplifying a target nucleic acid sequence contained in a template nucleic acid, the method comprising:

(a) preparing a template nucleic acid containing a target nucleic acid sequence;

(b) preparing a primer set according to ~~any one of claims 1 to 7~~ claim 1; and

(c) performing a nucleic acid amplification reaction in the presence of the template nucleic acid using the primer set.

9. (ORIGINAL) The method according to claim 8, wherein the nucleic acid amplification reaction is performed isothermally.

10. (ORIGINAL) The method according to claim 8, wherein a polymerase having strand displacement ability is used.

11. (ORIGINAL) The method according to claim 8, wherein the nucleic acid amplification reaction is performed in the presence of a melting temperature adjusting agent.

12. (ORIGINAL) The method according to claim 11, wherein the melting temperature adjusting agent is dimethyl sulfoxide, betaine, formamide, glycerol, or a mixture of two or more of them.

13. (ORIGINAL) The method according to claim 8, wherein the nucleic acid amplification reaction is performed in the presence of an enzyme stabilizing agent.

14. (ORIGINAL) The method according to claim 13, wherein the enzyme stabilizing agent is trehalose, sorbitol, mannitol, or a mixture of two or more of them.

15. (CURRENTLY AMENDED) A method of determining the presence or absence of a mutation in a nucleic acid sequence contained in a nucleic acid sample, the method comprising:

(a) preparing a nucleic acid sample;

(b) preparing a primer set according to ~~any one of claims 1 to 7~~ claim 1 that is designed so that a nucleic acid sequence with or without the mutation serves as a target nucleic acid sequence, and a nucleotide residue associated with the mutation is contained in a sequence (A), a sequence (B), or a sequence (C); and

(c) performing a nucleic acid amplification reaction in the presence of the nucleic acid sample using the primer set.

16. (ORIGINAL) The method according to claim 15, wherein in the process (b), a primer set is prepared that is designed so that the nucleotide residue associated with the mutation is contained in the sequence (A).

17. (ORIGINAL) The method according to claim 15, wherein in the process (b), a primer set is prepared that is designed so that the nucleotide residue associated with the mutation is contained in the sequence (B).

18. (ORIGINAL) The method according to claim 15, wherein in the process (b), a primer set is prepared that is designed so that the nucleotide residue associated with the mutation is contained in the sequence (C).

19. (ORIGINAL) The method according to claim 15, wherein the nucleic acid amplification reaction is performed in the presence of a mismatch binding protein.

20. (ORIGINAL) The method according to claim 15, wherein the nucleic acid amplification reaction is performed isothermally.

21. (ORIGINAL) The method according to claim 15, wherein a polymerase having strand displacement ability is used.

22. (ORIGINAL) The method according to claim 15, wherein the nucleic acid amplification reaction is performed in the presence of a melting temperature adjusting agent.

23. (ORIGINAL) The method according to claim 22, wherein the melting temperature adjusting agent is dimethyl sulfoxide, betaine, formamide, glycerol, or a mixture of two or more of them.

24. (ORIGINAL) The method according to claim 15, wherein the nucleic acid amplification reaction is performed in the presence of an enzyme stabilizing agent.

25. (ORIGINAL) The method according to claim 24, wherein the enzyme stabilizing agent is trehalose, sorbitol, mannitol, or a mixture of two or more of them.

26. (CURRENTLY AMENDED) A method of determining the presence or absence of a deletion or insertion of a sequence in a nucleic acid sequence contained in a nucleic acid sample, the method comprising:

(a) preparing a nucleic acid sample;

(b) preparing a primer set according to ~~any one of claims 1 to 7~~ claim 1 that is designed so that a nucleic acid sequence with or without a sequence associated with a deletion or insertion serves as a target nucleic acid sequence, and a site associated with the deletion or insertion is contained in a sequence (A), a sequence (B), or a sequence (C), or is positioned between the sequence (A) and the sequence (B) or between the sequence (A) and the sequence (C); and

(c) performing a nucleic acid amplification reaction in the presence of the nucleic acid sample using the primer set.

27. (ORIGINAL) The method according to claim 26, wherein in the process (b), a primer set is prepared that is designed so that the site associated with the deletion or insertion is positioned between the sequence (A) and the sequence (B).

28. (ORIGINAL) The method according to claim 26, wherein the sequence associated with the deletion or insertion is an intronic sequence that is contained in a gene on a genome.

29. (ORIGINAL) The method according to claim 26, wherein the target nucleic acid sequence is mRNA.

30. (ORIGINAL) The method according to claim 26, wherein the nucleic acid amplification reaction is performed isothermally.

31. (ORIGINAL) The method according to claim 26, wherein a polymerase having strand displacement ability is used.

32. (ORIGINAL) The method according to claim 26, wherein the nucleic acid amplification reaction is performed in the presence of a melting temperature adjusting agent.

33. (ORIGINAL) The method according to claim 32, wherein the melting temperature adjusting agent is dimethyl sulfoxide, betaine, formamide, glycerol, or a mixture of two or more of them.

34. (ORIGINAL) The method according to claim 26, wherein the nucleic acid amplification reaction is performed in the presence of an enzyme stabilizing agent.

35. (ORIGINAL) The method according to claim 34, wherein the enzyme stabilizing agent is trehalose, sorbitol, mannitol, or a mixture of two or more of them.

36. (ORIGINAL) A method of determining the presence or absence of a mutation in a nucleic acid sequence contained in a nucleic acid sample, the method comprising:

(a) preparing a nucleic acid sample;

(b) preparing a primer set that allows a target nucleic acid sequence containing a site associated with a mutation to be amplified, the primer set being designed so that when at least one primer included in the primer set hybridizes to a nucleic acid sequence contained in the nucleic acid sample or a complementary sequence thereto, at least one mismatch occurs between the at least one primer and the nucleic acid sequence or the complementary sequence thereto, depending on the presence or absence of the mutation; and

(c) performing a nucleic acid amplification reaction in the presence of a substance having mismatch recognition ability, using the primer set in which the nucleic acid sample serves as a template.

37. (ORIGINAL) The method according to claim 36, wherein the primer set allows the target nucleic acid sequence to be amplified isothermally, and the nucleic acid amplification reaction is performed isothermally.

38. (ORIGINAL) The method according to claim 36, wherein the substance having mismatch recognition ability is a mismatch binding protein.

39. (ORIGINAL) The method according to claim 38, wherein the mismatch binding protein is MutS, MSH2, MSH6, or a mixture of two or more of them.

40. (ORIGINAL) The method according to claim 36, wherein a first primer included in the primer set contains, in its 3' end portion, a sequence (Ac') that hybridizes to a sequence (A) located in the 3' end portion of the target nucleic acid sequence, and also contains, on the 5' side of the sequence (Ac'), a sequence (B') that hybridizes to a complementary sequence (Bc) to a sequence (B) that is present on the 5' side with respect to the sequence (A) in the target nucleic acid sequence.

41. (ORIGINAL) The method according to claim 40, wherein the first primer is designed so that at least one mismatch occurs between the sequence (A) and the sequence (Ac'), depending on the presence or absence of the mutation.

42. (ORIGINAL) The method according to claim 40, wherein the first primer is designed so that at least one mismatch occurs between the sequence (Bc) and the sequence (B'), depending on the presence or absence of the mutation.

43. (ORIGINAL) The method according to claim 36, wherein a second primer included in the primer set contains, in its 3' end portion, a sequence (Cc') that hybridizes to a sequence (C) located in the 3' end portion of a complementary sequence to the target nucleic acid sequence, and also contains, on the 5' side of the sequence (Cc'), a folded sequence (D-Dc') that contains, on the same strand, two nucleic acid sequences that hybridize to each other.

44. (ORIGINAL) The method according to claim 43, wherein the second primer is designed so that at least one mismatch occurs between the sequence (C) and the sequence (Cc'), depending on the presence or absence of the mutation.

45. (ORIGINAL) The method according to claim 36, wherein the primer set further comprises a third primer that hybridizes to the target nucleic acid sequence or a complementary sequence thereto and that does not compete with other primers for hybridization to the target nucleic acid sequence or the complementary sequence thereto.

46. (ORIGINAL) The method according to claim 45, wherein the third primer is designed so that when the third primer hybridizes to the nucleic acid sequence contained in the nucleic acid sample or the complementary sequence thereto, at least one mismatch occurs between the third primer and the nucleic acid sequence or the complementary sequence thereto, depending on the presence or absence of the mutation.

47. (ORIGINAL) The method according to claim 36, wherein a polymerase having strand displacement ability is used.

48. (ORIGINAL) The method according to claim 36, wherein the nucleic acid amplification reaction is performed in the presence of a melting temperature adjusting agent.

49. (ORIGINAL) The method according to claim 48, wherein the melting temperature adjusting agent is dimethyl sulfoxide, betaine, formamide, glycerol, or a mixture of two or more of them.

50. (ORIGINAL) The method according to claim 36, wherein the nucleic acid amplification reaction is performed in the presence of an enzyme stabilizing agent.

51. (ORIGINAL) The method according to claim 50, wherein the enzyme stabilizing agent is trehalose, sorbitol, mannitol, or a mixture of two or more of them.

52. (ORIGINAL) A kit for determining the presence or absence of a mutation in a nucleic acid sequence contained in a nucleic acid sample, the kit comprising:
(a) a substance having mismatch recognition ability; and
(b) a primer set that allows a target nucleic acid sequence containing a site associated with a mutation to be amplified, at least one primer included in the primer set being designed so that when the at least one primer hybridizes to the nucleic acid sequence contained in the nucleic acid sample or a complementary sequence thereto, at least one mismatch occurs between the at least one primer and the nucleic acid sequence or the complementary sequence thereto, depending on the presence or absence of the mutation.

53. (ORIGINAL) The kit according to claim 52, wherein the primer set allows the target nucleic acid sequence to be amplified isothermally.

54. (ORIGINAL) The kit according to claim 52, wherein the substance having mismatch recognition ability is a mismatch binding protein.

55. (ORIGINAL) The kit according to claim 54, wherein the mismatch binding protein is MutS, MSH2, MSH6, or a mixture of two or more of them.

56. (ORIGINAL) The kit according to claim 52, wherein a first primer included in the primer set contains, in its 3' end portion, a sequence (Ac') that hybridizes to a sequence (A) located in the 3' end portion of the target nucleic acid sequence, and also contains, on the 5' side of the sequence (Ac'), a sequence (B') that hybridizes to a complementary sequence (Bc) to a sequence (B) that is present on the 5' side with respect to the sequence (A) in the target nucleic acid sequence.

57. (ORIGINAL) The kit according to claim 56, wherein the first primer is designed so that at least one mismatch occurs between the sequence (A) and the sequence (Ac'), depending on the presence or absence of the mutation.

58. (ORIGINAL) The kit according to claim 56, wherein the first primer is designed so that at least one mismatch occurs between the sequence (Bc) and the sequence (B'), depending on the presence or absence of the mutation.

59. (ORIGINAL) The kit according to claim 52, wherein a second primer included in the primer set contains, in its 3' end portion, a sequence (Cc') that hybridizes to a sequence (C) located in the 3' end portion of a complementary sequence to the target nucleic acid sequence, and also contains, on the 5' side of the sequence (Cc'), a folded sequence (D-Dc') that contains, on the same strand, two nucleic acid sequences that hybridize to each other.

60. (ORIGINAL) The kit according to claim 59, wherein the second primer is designed so that at least one mismatch occurs between the sequence (C) and the sequence (Cc'), depending on the presence or absence of the mutation.

61. (ORIGINAL) The kit according to claim 52, further comprising a third primer that hybridizes to the target nucleic acid sequence or a complementary sequence thereto, wherein the third primer does not compete with other primers for hybridization to the target nucleic acid sequence or the complementary sequence thereto.

62. (ORIGINAL) The kit according to claim 61, wherein the third primer is designed so that when the third primer hybridizes to the nucleic acid sequence contained in the nucleic acid sample or the complementary sequence thereto, at least one mismatch occurs between the third primer and the nucleic acid sequence or the complementary sequence thereto, depending on the presence or absence of the mutation.

63. (ORIGINAL) The kit according to claim 52, further comprising a polymerase having strand displacement ability.

64. (ORIGINAL) A method of determining the presence or absence of a mutation in a nucleic acid sequence contained in a nucleic acid sample, the method comprising:

(a) preparing a nucleic acid sample;

(b) preparing a primer set that allows a target nucleic acid sequence containing a site associated with a mutation to be amplified;

(c) preparing a nucleic acid fragment that hybridizes to the target nucleic acid sequence and that is designed so that when the nucleic acid fragment hybridizes to a nucleic acid sequence contained in the nucleic acid sample or a complementary sequence thereto, at least one mismatch occurs between the nucleic acid fragment and the nucleic acid sequence or the complementary sequence thereto, depending on the presence or absence of the mutation; and

(d) performing a nucleic acid amplification reaction in the presence of a substance having mismatch recognition ability and the nucleic acid fragment, using the primer set in which the nucleic acid sample serves as a template.

65. (ORIGINAL) The method according to claim 64, wherein the primer set allows the target nucleic acid sequence to be amplified isothermally, and the nucleic acid amplification reaction is performed isothermally.

66. (ORIGINAL) The method according to claim 64, wherein the substance having mismatch recognition ability is a mismatch binding protein.

67. (ORIGINAL) The method according to claim 66, wherein the mismatch binding protein is MutS, MSH2, MSH6, or a mixture of two or more of them.

68. (ORIGINAL) The method according to claim 64, wherein a first primer included in the primer set contains, in its 3' end portion, a sequence (Ac') that hybridizes to a sequence (A) located in the 3' end portion of the target nucleic acid sequence, and also contains, on the 5' side of the sequence (Ac'), a sequence (B') that hybridizes to a complementary sequence (Bc) to a sequence (B) that is present on the 5' side with respect to the sequence (A) in the target nucleic acid sequence.

69. (ORIGINAL) The method according to claim 64, wherein a second primer included in the primer set contains, in its 3' end portion, a sequence (Cc') that hybridizes to a sequence (C) located in the 3' end portion of a complementary sequence to the target nucleic acid sequence, and also contains, on the 5' side of the sequence (Cc'), a folded sequence (D-Dc') that contains, on the same strand, two nucleic acid sequences that hybridize to each other.

70. (ORIGINAL) The method according to claim 64, wherein the primer set further comprises a third primer that hybridizes to the target nucleic acid sequence or a complementary sequence thereto and that does not compete with other primers for hybridization to the target nucleic acid sequence or the complementary sequence thereto.

71. (ORIGINAL) The method according to claim 64, wherein a polymerase having strand displacement ability is used.

72. (ORIGINAL) The method according to claim 64, wherein the nucleic acid amplification reaction is performed in the presence of a melting temperature adjusting agent.

73. (ORIGINAL) The method according to claim 72, wherein the melting temperature adjusting agent is dimethyl sulfoxide, betaine, formamide, glycerol, or a mixture of two or more of them.

74. (ORIGINAL) The method according to claim 64, wherein the nucleic acid amplification reaction is performed in the presence of an enzyme stabilizing agent.

75. (ORIGINAL) The method according to claim 74, wherein the enzyme stabilizing agent is trehalose, sorbitol, mannitol, or a mixture of two or more of them.

76. (ORIGINAL) A kit for determining the presence or absence of a mutation in a nucleic acid sequence contained in a nucleic acid sample, the kit comprising:

(a) a substance having mismatch recognition ability; and

(b) a primer set that allows a target nucleic acid sequence containing a site associated with a mutation to be amplified; and

(c) a nucleic acid fragment that hybridizes to the target nucleic acid sequence, the nucleic acid fragment being designed so that when the nucleic acid fragment hybridizes to the nucleic acid sequence contained in the nucleic acid sample or a complementary sequence thereto, at least one mismatch occurs between the nucleic acid fragment and the nucleic acid sequence or the complementary sequence thereto, depending on the presence or absence of the mutation.

77. (ORIGINAL) The kit according to claim 76, wherein the primer set allows the target nucleic acid sequence to be amplified isothermally.

78. (ORIGINAL) The kit according to claim 76, wherein the substance having mismatch recognition ability is a mismatch binding protein.

79. (ORIGINAL) The kit according to claim 78, wherein the mismatch binding protein is MutS, MSH2, MSH6, or a mixture of two or more of them.

80. (ORIGINAL) The kit according to claim 76, wherein a first primer included in the primer set contains, in its 3' end portion, a sequence (Ac') that hybridizes to a sequence (A) located in the 3' end portion of the target nucleic acid sequence, and also contains, on the 5' side of the sequence (Ac'), a sequence (B') that hybridizes to a complementary sequence (Bc) to a sequence (B) that is present on the 5' side with respect to the sequence (A) in the target nucleic acid sequence.

81. (ORIGINAL) The kit according to claim 76, wherein a second primer included in the primer set contains, in its 3' end portion, a sequence (Cc') that hybridizes to a sequence (C) located in the 3' end portion of a complementary sequence to the target nucleic acid sequence, and also contains, on the 5' side of the sequence (Cc'), a folded

sequence (D-Dc') that contains, on the same strand, two nucleic acid sequences that hybridize to each other.

82. (ORIGINAL) The kit according to claim 76, wherein the primer set further comprises a third primer that hybridizes to the target nucleic acid sequence or a complementary sequence thereto, and the third primer does not compete with other primers for hybridization to the target nucleic acid sequence or the complementary sequence thereto.

83. (ORIGINAL) The kit according to claim 76, further comprising a polymerase having strand displacement ability.

REMARKS

The above preliminary amendment is made to remove multiple dependencies from claims 8, 15, 26, 36, 52, 64 and 76.

Applicants respectfully request that the preliminary amendment described herein be entered into the record prior to calculation of the filing fee and prior to examination and consideration of the above-identified application.

If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicants' primary attorney-of record, Douglas P. Mueller (Reg. No. 30,300), at (612) 455.3804.

Respectfully submitted,

HAMRE, SCHUMANN, MUELLER & LARSON, P.C.
P.O. Box 2902-0902
Minneapolis, MN 55402-0902
(612) 455-3800

Dated: March 22, 2007

By: _____
Douglas P. Mueller
Reg. No. 30,300

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HAMRE, SCHUMANN, MUELLER & LARSON, P.C.

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225 SOUTH SIXTH STREET · SUITE 2650 · MINNEAPOLIS · MN 55402
TEL. 612.455.3800 · FAX 612.455.3801
WWW.HSML.COM · MAIL@HSML.COM